

## RESEARCH ARTICLE

# Microvascular Alterations in Hypertension and Vascular Aging

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**Abstract:** Hypertension and aging are characterized by vascular remodelling and stiffness as well as endothelial dysfunction. Endothelial function declines with age, since aging is associated with senescence of the endothelium due to increased rate of apoptosis and reduced regenerative capacity of the endothelium. Different phenotypes of hypertension have been described in younger and adult subjects with hypertension. In younger patients, functional and structural alterations of resistance arteries occur as the earliest vascular alterations which have prognostic significance and may contribute to stiffness of large arteries through wave reflection. In individuals above age of 50 years as well as in subjects with long-lasting elevated blood pressure, vascular changes occur predominantly in conduit arteries which become stiffer. Activation of renin-angiotensin-aldosterone and endothelin systems plays a key role in endothelial dysfunction, vascular remodelling, and aging by inducing reactive oxygen species production, and promoting inflammation and cell growth.

**Keywords:** Vascular remodelling, media-to-lumen ratio, arterial stiffness, PWV, pulse pressure, endothelial dysfunction.

## INTRODUCTION

Hypertension and cardiovascular disease increase with advancing age as shown in epidemiological studies. In particular, hypertension is an important risk factor for vascular senescence [1], resulting in premature cardiovascular disease.

In younger patients, increased peripheral vascular resistance is a common feature of essential hypertension. In presence of elevated blood pressure, vascular remodelling may occur over time particularly in the wall of large arteries through sustained stretch on the vascular wall which activates distinctive intracellular pathways [2], resulting in structural and functional alterations that eventually induce vascular stiffness, increased systolic blood pressure and may contribute to the progression of atherosclerosis [3].

In this regard, hypertensive vascular alterations and the age-associated changes in blood vessels share similar phenotypes, including structural changes (increased arterial wall thickness and stiffness as well as reduced compliance and lumen diameter) [1, 4], vascular inflammation [5, 6], and impaired endothelial function due to increased oxidative stress and decreased production of vasodilator agents such as nitric oxide (NO) [7].

Alterations in vascular tone at level of resistance arteries play an important role in the pathophysiology of hypertension by increasing peripheral resistance which is the most important site of pulse wave reflection that contributes to the stiffness of large arteries [3]. Impaired endothelial function is a common feature of hypertension and largely participates in the increased constriction of resistance arteries [8]. Also aging contributes to endothelial dysfunction which is characterized by reduced vasodilation and increased endothelium-dependent contraction, vascular permeability and a pro-inflammatory and prothrombotic phenotype. The latter is characterized by leucocyte-endothelial interactions that participate in vascular inflammation and increased adhesion and platelet aggregation [9-11], and it is recognized to be inde-

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pendently associated with increased cardiovascular risk [12]. The activation of inflammatory process in vascular and perivascular tissue is recognized as an important determinant in the pathophysiology of the structural alterations in the vascular wall of resistance and large arteries [13]. This may contribute to the development of the increased vascular resistance and vascular stiffness in large arteries as well as to the development of atherosclerosis [14, 15]. Vascular stiffness can be evaluated by carotid-femoral pulse wave velocity (PWV), that is associated with target organ damage and increased risk for cardiovascular morbidity and mortality [16].

It is well assessed that renin-angiotensin system (RAS) plays a key role in the pathophysiology of hypertension [17], contributing to oxidative stress, vascular inflammation, and thus to endothelial dysfunction.

This review will focus on the alterations that occur in the vascular wall particularly in resistance arteries (lumen diameter of 100-300  $\mu\text{m}$ ) in hypertension and vascular aging.

## ENDOTHELIAL DYSFUNCTION

The endothelium may be considered the largest organ in the body as it is able to generate several factors that regulate vascular tone, vascular permeability, angiogenesis, and the response to inflammation. NO is the main modulator of endothelial function since it induces vasodilation, and exerts antioxidant and antiinflammatory function [18], by inhibiting leukocyte adhesion [19], thrombocyte aggregation [20] and smooth muscle cell proliferation [21].

Endothelial dysfunction is characterized by the impairment of endothelium-induced vasodilation, enhanced vasoconstriction and increased production of reactive oxygen species (ROS), thus it may contribute to the inflammation of the vascular wall [9, 11, 16, 17, 22, 23] and therefore to the remodelling of the arterial wall that typically occurs in hypertension as well in aging.

Endothelial dysfunction is one of the most important age-associated cardiovascular changes [24, 25], that may occur in association with other important cardiovascular risk factors such as hypertension, diabetes dyslipidemia, and obesity.

Endothelium-dependent vasodilatation progressively declines with age as assessed by several clinical and experimental studies in different vascular beds including resistance arteries [25-29]. This may contribute to the development of hypertension as well to the hypertension related vascular alterations. Several putative mechanisms have been advocated to explain this effect including the breakdown of NO and other endothelial-derived substances such as prostacyclin and the endothelium-derived hyperpolarizing factor (EDHF) [30], independently of the structural changes in the vascular wall [31-38]. This, in turn, is associated with an enhanced reactivity to vasoconstrictors [39]. It has been reported that endothelial NO synthase (eNOS) expression and NO production decline with age [35, 40-42]. This may occur through the reduced eNOS mRNA expression and stability [43] due to the age-related decrease in shear stress [44] as well as by the age-related reduction of growth factors including human growth hormone (GH) [45]. Interestingly, physical training as well as therapy with GH improves eNOS ex-

pression and endothelial function in aged rats [42, 46] and humans [47-49].

Aging is associated with increased ROS production particularly in endothelial cells. Indeed, removal of the endothelium and the inhibition of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (the main source of ROS in the vasculature) reduce vascular superoxide generation in the aorta of aged rats [50-55].

The increased production of ROS in the vasculature contributes to the reduced NO bioavailability and to the impaired relaxation [35, 38, 50] particularly in the microcirculation [39]. This may occur through the uncoupling of the eNOS [35] and the generation of peroxynitrite [35, 56], which is a highly reactive oxidizing agent [57]. In fact, peroxynitrite is able to penetrate across cellular membranes and by substrate nitration, it may inactivate different enzymes, including free radical scavengers [35, 58]. Thus, the increased formation of peroxynitrite and reduced NO bioavailability during aging may inactivate antioxidative enzymes including superoxide dismutase (SOD) [56, 59]. Therefore, also cellular antioxidative defense systems are attenuated with aging [60]. This can further contribute to the enhanced production of ROS and endothelial dysfunction. Furthermore, it has been shown that the expression of inducible NO synthase (iNOS) is enhanced within the vascular wall of aged rats [35, 61]. iNOS further promotes oxidative stress through the enhanced generation of superoxide anion and the formation of peroxynitrite [57, 62]. ROS is also produced by mitochondria [63-69] and contributes to mitochondrial dysfunction which is progressively increased in vascular aging. In particular, it has been shown that mice lacking the mitochondrial p66Shc adaptor protein presented reduced production of intracellular ROS, increased NO bioavailability and improved endothelial dysfunction [70]. These features are associated with no age-dependent changes in iNOS as well as with prolonged life span [71]. Thus, the modulation of p66Shc function could be relevant for the protection from age-dependent endothelial dysfunction.

Vascular senescence is also associated with reduced capacity of the endothelium to regenerate [72-74]. Under normal conditions, endothelial cells present a low turnover rate [75], with aging endothelial cells expressing negative cell cycle regulators (*i.e.* p53 and p16) [76-79], and are characterized by impaired secretion of and/or sensitivity to growth factors which lead to growth arrest and senescence. Moreover, aged endothelial cells show also suppressed activity of telomerase reverse transcriptase [80-82], which is associated with shorter telomere length that is inversely related to chronological age in endothelial cells [80, 81]. Interestingly, RAS activation and increased ROS production contribute to the reduction of the telomerase activity as well as to DNA damage and genomic instability. These are all-important promoters of cellular senescence [83-88] in the vasculature.

Also angiogenesis reduces with aging; in particular, endothelial senescence may be responsible for some processes that are typically observed in the elderly such as the impaired wound healing and angiogenesis [89]. In experimental model of senescence both in mice and humans, an imbalance between pro-angiogenic and anti-angiogenic factors has been

described, particularly in microvascular endothelial cells. Specifically, the pro-angiogenic factors such as tissue inhibitor of metalloproteinase-2 (TIMP-2) [90] and the thrombospondin-2 [91] are increased, whereas, the anti-angiogenic factors such as vascular endothelial growth factor (VEGF) and transforming growth factor- $\beta$  1 (TGF- $\beta$ 1) are reduced. These alterations are associated with reduced matrix deposition and reduced angiogenesis-associated inflammation which are required for angiogenesis. Moreover, also circulating endothelial progenitor cells (EPCs) are an important determinant for the potential capacity of endothelium regeneration as well as of endothelial function. EPCs are significantly reduced in aging [92] as well as in hypertensive conditions [93, 94]. Finally, decreased EPCs numbers are also associated with decreased endothelial function [94] and arterial stiffness [95].

## REMODELLING OF RESISTANCE ARTERIES

Vascular remodelling is typically found in resistance arteries of hypertensive individuals and is characterized by reduced vascular lumen with increased media thickness (*i.e.* increased media-to-lumen ratio - M/L-). These alterations may be functional, mechanical and/or structural [3, 96]. It has been well documented that M/L is considered the most reproducible parameter of vascular remodelling of resistance arteries [3, 97]. A smaller lumen and the increased media thickness decrease circumferential tension and reduce media stress in order to protect the wall of the artery from the effects of elevated blood pressure. On the other hand, small decreases in the lumen diameter significantly increase resistance to blood flow, which can contribute to maintaining elevated blood pressure values. Interestingly, increased M/L ratio is associated with the occurrence of cardiovascular events [98]. It is thought that increased M/L ratio could be the earliest alteration that occurs in the vasculature [99], and may precede endothelial dysfunction in hypertensive patients. Among the factors that may contribute to the structural alterations of the arterial wall, the variation of myogenic tone (*i.e.* the intrinsic ability of vessels to constrict in response to increased intraluminal pressure) may exert a significant contribution [100]. Moreover, increased concentration of specific agonists including Ang II and endothelin may also contribute to vasoconstriction and vascular remodelling by increasing the intracellular calcium levels, protein kinases, diacylglycerol, ROS generation [100, 101], and extracellular matrix deposition. These alterations may occur in hypertension as well as in aging. With chronic vasoconstriction, vessels may become embedded in a remodelled extracellular matrix and may not return to their dilated state [3, 100], and in turn, structural narrowing of the lumen may amplify vasoconstriction. Two different types of vascular remodelling have been described: eutrophic and hypertrophic vascular remodelling. Hypertrophic remodelling is characterized by the increased M/L together with increased media cross-sectional area, whereas in eutrophic remodelling, the media cross-section does not increase [3, 97], rather smooth muscle cells are reorganized around a smaller lumen which leads to increased M/L. Although both eutrophic and hypertrophic remodelling may occur in the same subject in different vascular beds, these types of vascular remodelling occur in distinct types of arterial hypertension. Eutrophic vascular

remodelling is generally found in mild-to-moderate hypertension and is also combined with enhanced apoptosis in the periphery of the vessel [101, 102]. In experimental animals, eutrophic remodelling is often associated with activation of the RAS. If hypertension is severe or longstanding as well as whether the myogenic reflex and the autoregulatory mechanisms are dysfunctional, the increase in the wall stress may induce hypertrophy. Hypertrophic remodelling of resistance arteries is more prevalent in renovascular hypertension [103], diabetic subjects [104, 105] and acromegalic patients [106], and may also occur in hyperaldosteronism.

## Mechanism of Vascular Remodelling

The molecular mechanisms involved in the remodelling of resistance arteries are not fully understood and are in part similar to those involved in vasculature aging. Several factors may be involved in this process including the activation of RAS, the enhancement of inflammation, growth and profibrotic processes, as well as the modification of VSMCs and extracellular matrix components [107]. The reorganization of the vessel wall components (including collagen, elastin, and other components of extracellular matrix) around a narrower lumen occurs in eutrophic remodelling of resistance arteries, whereas cell growth and deposition of extracellular matrix components contribute to media thickening in hypertrophic remodelling [108-110]. Cell growth and extracellular matrix deposition may result from blood pressure elevation and/or from growth-promoting factors including Ang II, endothelin-1, and catecholamines. Several experimental data have shown that also the reduced activity of matrix metalloproteinases (MMPs) may play a role in the remodelling of the extracellular matrix in the vascular wall. MMP-1 is reduced in the serum of hypertensive patients with increased vascular level of type I collagen [111] as well as MMP-2 and MMP-3 activity are reduced in spontaneously hypertensive rats [112]. Furthermore, the decrease of MMPs activity in resistance arteries is associated with accumulation of collagen type IV and V and fibronectin [113]. Moreover, in rat mesenteric arteries, MMP-2 is associated with the reduction of the vasoconstrictor effects of the precursor of endothelin-1, the big endothelin-1 [114]. This may contribute to endothelial dysfunction, vasospasm, blood pressure elevation and its related cardiovascular complications. [115]. Moreover, in vascular aging, particularly in large arteries, polymorphisms of MMP-3 and MMP-9 have been associated with vascular remodelling and arterial stiffness [116, 117]. VSMCs are multifunctional cells, which significantly contribute to vascular function and tone. Alteration of VSMCs is associated to arterial remodelling in aging and hypertension through different mechanisms, including hyperplasia, cell growth, apoptosis, cell elongation and reorganization as well as to new production of extracellular matrix proteins, inflammation of the arterial wall, and fibrosis [118-121]. Detachment of VSMCs and endothelial cells, decreased endothelial progenitor cells, and increased microparticles may further contribute to vascular dysfunction and remodelling [111, 122, 123]. Apoptosis is an important mechanism that may contribute to structural remodelling of the arterial wall in aging and hypertension [111, 123], although its role is not fully understood. In particular, apoptosis could be either a primary event that may occur in the vasculature in hypertensive con-

ditions and aging or may be part of a growth-associated compensatory process. Thus an imbalance between growth and apoptosis could be relevant in vascular remodelling.

RAS activation plays a key role in the pathophysiology of vascular remodelling [2]. Ang II may induce vascular remodelling by several mechanisms including vasoconstriction, cell growth, oxidative stress and inflammation. Mainly in hypertensive conditions, Ang II and aldosterone, as well as endothelin-1 enhance the basal superoxide production by the activation of NADPH oxidase and expression of its subunits *via* the activation of cSrc, PKC (protein kinase C), PLA2 (phospholipase A2) and PLD (phospholipase D) pathways [8, 124-126]. Increased ROS production contributes to the development of vascular dysfunction and arterial remodelling in part by impairing endothelium-derived NO bioavailability as well as by inducing VSMCs proliferation and hypertrophy, collagen deposition in the vascular wall and by inducing the release of pro-inflammatory cytokine and transcription factors (*i.e.* NF- $\kappa$ B). These processes may lead to the functional and structural changes in the circulation, and may participate in the development and progression of atherosclerosis in large arteries.

RAS activity is potentiated by the activation of mineralocorticoid receptors that may contribute to inflammation, fibrosis and vascular dysfunction and damage. In this regard, aldosterone enhances the activity of tissue angiotensin-converting enzyme [125] and up-regulates angiotensin receptors [126] as well as aldosterone induces ROS formation and endothelial dysfunction in several organs including heart and brain, as described in different experimental settings in animal models of cardiovascular disease [126]. Thus, mineralocorticoid antagonism may attenuate these deleterious effects by reducing directly the pro-inflammatory and pro-fibrotic effects of aldosterone [127, 128].

Importantly, inflammation of the vascular wall participates in vascular remodelling by promoting the cell growth and VSMCs proliferation, thus contributing to the accelerated vascular damage in aging and in hypertensive conditions [13], as well as to the initiation and progression of atherosclerosis and the development of cardiovascular and cerebrovascular diseases [14, 15, 129, 130]. In the context of inflammation, an important role is played by adhesion molecules (VCAM-1, ICAM-1) which are increased on the endothelial cell membrane at the early stage of the inflammatory process. This leads to the accumulation of monocyte/macrophages, and lymphocytes [131] in the arterial wall.

Also perivascular fat is involved in vascular remodelling since it exhibits inflammatory changes characterized by increased generation of inflammatory mediators such as Tumor Necrosis Factor (TNF)-alpha and increased production of oxidative stress, as well as reduced adiponectin production that may contribute to a contractile phenotype [132, 133].

A large body of evidence indicates that innate immunity may be involved in the mechanisms that contribute to the vascular inflammation, particularly in hypertension. Experimental data showed that the reduction of Treg and the impairment T effector upregulation are associated with in-

creased blood pressure and are involved in the pathogenesis of blood pressure-induced vascular inflammation and cardiovascular remodelling. In this regard, an imbalance between pro-inflammatory subsets of T lymphocytes (Th1, Th2 and Th17) and the anti-inflammatory T regulatory (Treg) cells might be in part responsible for the inflammatory response in cardiac and metabolic diseases [134]. It has been shown that Ang II and increased ROS production are important modulators of T-cell activation [135-139] as well as Treg cells adoptive transfer may exert a blood pressure lowering effect and modulation of vascular remodelling in mice infused with either AngII [136] or aldosterone [137]. Furthermore, mice deficient in vascular macrophages and in T- and B- lymphocytes did not present vascular remodelling in response to Ang II- or DOCA-salt [13, 135].

Rarefaction is a different type of remodelling process which occurs in hypertension and aging at the level of smaller arterioles (lumen diameter <40  $\mu$ ) [3]. With this process, the density of arterioles per unit of tissue is reduced, thus vascular resistance is increased [140]. In particular, in hypertension, vasoconstriction may induce a functional reduction of small arterioles that may become anatomically permanent, resulting in decreased tissue perfusion.

## CONTRIBUTION OF THE INCREASED PERIPHERAL RESISTANCE TO THE REMODELLING OF CONDUIT ARTERIES

Aging and elevated blood pressure are the two major determinants of increased arterial stiffness in conduit arteries [41]. In patients with long lasting hypertension, or in adult subjects (age >50 years), large conduit arteries such as aorta become stiffer because of age-related processes which significantly contribute to systolic blood pressure increase. Interestingly with aging, diastolic blood pressure tends to decrease, leading to increased pulse pressure (PP). In younger individuals, who have a more elastic arterial wall in conduit arteries, PP increases from central to peripheral arteries. This is due to the summation of the incident and the reflected waves more distantly along compliant arteries. Reflected waves originate at different vascular sites from the peripheral vasculature, mainly in resistance sites. In an elastic and compliant vasculature, reflected waves return towards the heart in diastole [141]. With aging, reflected waves return at faster velocity in stiffer arteries, as well as the forward waves from the heart toward the periphery are accelerated, thus the net result is the earlier summation of both forward and reflected waves in the cardiac cycle, leading to the amplification and increase of the aortic systolic pressure. This augmentation contributes to the absence of amplification toward the periphery, which is associated to the increased aortic and peripheral systolic blood pressure and PP. Moreover, it contributes further to the increased stiffness of central elastic arteries. Hypertension may accelerate these mechanisms. Resistance arteries may play a determinant role in this process as the remodelled resistance arteries are not only the site of vascular resistance but possibly the origin of large part of wave reflection in aorta [142]. In turn, increased stiffness and pulsatility in aorta are transmitted to resistance arteries and may contribute to vascular injury in this vascular district [143]. The velocity of propagation of the pressure

wave along the conduit arteries may be measured through the PWV by tonometric evaluation [142]. Aortic PWV increases with advancing age and is probably the most accurate measure available of aortic stiffness. [144].

A possible association between indices of conduit arterial stiffness and M/L ratio of resistance arteries has been described [145]. M/L ratio was significantly related to brachial systolic blood pressure and PP and to central systolic blood pressure and PP. Moreover, a positive correlation was observed between M/L ratio and carotid femoral PWV independently of age and mean blood pressure [145]. A link between extracellular matrix molecules and aortic stiffness has also been described. Aortic stiffness is correlated with the expression of genes involved in increased vascular tone and remodelling and in long term sustained contraction (*i.e.* protein phosphatase-1, the catalytic subunit of myosin light chain phosphatase, members of the family of A kinase anchor protein) [146, 147] as well as with deposition of collagen, fibronectin and non-fibrillar extracellular material in the media. The increase in aortic stiffness and reduced compliance of conduit arteries may contribute to the increase in central pressure and to the development of isolated systolic hypertension (ISH) that represents the most common type of hypertension in the elderly [16].

## CONCLUSION

Hypertension and aging share similar mechanisms of vascular dysfunction. Vascular remodelling, endothelial dysfunction and vascular stiffness are common features in hypertension and aging. Several agonists may contribute to these alterations observed in the vasculature in hypertension and aging. The activation of RAS plays a central role in the genesis of endothelial dysfunction and vascular remodelling by activating redox-sensitive pathways and promoting cell growth and inflammation. Functional and structural alterations of resistance arteries may represent the earliest vascular alterations in hypertensive patients which can contribute to maintain the increased blood pressure values over time, since small arteries and arterioles are the site of vascular resistance to blood flow. Moreover, resistance arteries are also considered the origin of most of the wave reflections contributing to the stiffness of large arteries and the increased central systolic blood pressure in the elderly. Thus, the alterations in the microvasculature may contribute and/or accelerate the aging of conduit arteries. Nevertheless, the relationship between the stiffness of conduit and microvascular dysfunction may be bidirectional, since the transmission of increased arterial pulsatility to resistance arteries could represent also a mechanism of damage at this level.

## DISCLOSURE

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## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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